CAN SYNAPTIC RESPONSE RATE DECREASE WITH INCREASING STIMULATION FREQUENCY? V. Matveev* and X.-J. Wang. Volen Center for Complex Systems, Brandeis University, Waltham, MA 02454.

Previous studies demonstrated that short-term depression may lead to saturation of the steady-state synaptic response rate $R_{ss}(r)$ at high stimulation rates (r), so that the synapse becomes independent of the frequency of sustained presynaptic firing, but sensitive to its temporal changes (Abbott et al, 1997; Tsodyks & Markram, 1997). More recently, at some cortical synapses $R_{ss}(r)$ was found to decrease with increasing r (Galarreta & Hestrin, 1998); it was suggested that this effect is important for stabilizing the activity of neuronal populations.

We have examined vesicle-release mechanisms at the presynaptic terminal that determine the behavior of the synaptic response, using computational approach. We investigated a vesicle turn-over model that includes two (docked and reserve) pools of vesicles. We found that the saturation behavior of $R_{ss}(r)$ at high r holds quite generally, and is not influenced by the specifics of the vesicle refill process. We find that the quantity which determines the dependence of $R_{ss}(r)$ on r is the *conditional* vesicle release probability, $p(r, N)$, given a fixed number N of available vesicles. Depending on the properties of $p(r, N)$, two different behaviors are possible: (i) $R_{ss}(r)$ reaches a non-zero stationary level at high r, if $p(r, N)$ does not depend on r, increases with increasing r, or decreases more slowly than $1/r$. (ii) if $p(r, N)$ decays faster than $1/r$ due to presynaptic processes other than vesicle depletion, $R_{ss}(r)$ decreases to zero at high r.

Our analysis indicates that neither vesicle depletion nor postsynaptic effects can explain the decay of $R_{ss}(r)$ at high r. We propose that inactivation of presynaptic Ca^{2+} channels provides a candidate mechanism for the $R_{ss}(r)$ decay: inactivation causes the $p(r, N)$ to decrease as an inverse power of rate, with the power roughly equal to the Ca^{2+}-cooperativity of neurotransmitter release.

(Supported by the NIH grant MH53717 and A. P. Sloan Foundation)